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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
24 February 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF MODULATION OF INTERACTION BETWEEN RECEPTOR AND LIGAND

(57) Abstract: The present invention relates to a method for modulating the interaction between at least two proteins, wherein at least one of the two proteins is a functional cell-surface receptor and the other protein is the receptor ligand. The invention features a binding site of said functional cell-surface receptor on the receptor ligand and discloses a series of amino acid sequences, which are part of the structure of said binding site and/or involved in the interaction between the receptor and the ligand. Moreover, the present invention features methods for molecular design and screening of a candidate compound capable of modulating the interaction between the functional cell-surface receptor and receptor ligand through the described binding site, and provides a screening assay for identification of such a compound. The invention further describes an antibody capable of binding to the above binding site and/or to an epitope comprising an amino acid sequence essential for executing the receptor ligand interaction through said binding site. The invention also concerns a variety of uses of the disclosed methods, peptide sequences and antibodies. The invention in preferred embodiments concerns the binding site of the fibroblast growth factor receptor (FGFR) on FGFR ligands, compounds capable of modulating the receptor ligand interaction through said binding site, and antibody capable of recognition of said binding site.

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INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/[redacted]3/00901

A. CLASSIFICATION OF SUBJECT MAT[redacted]
IPC 7 G01N33/566 C07K7/00 //A61K38/00,C07K14/71

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, SEQUENCE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03 016351 A (SKLADCHIKOVA GALINA ;BOCK ELISABETH (DK); BEREZIN VLADIMIR (DK); E) 27 February 2003 (2003-02-27) See SEQ ID NO:1 ---	1-44, 48-54
X	WO 97 38708 A (GEN HOSPITAL CORP ;SONG HEEKYUNG (US); WANG YUYING (US); GOETINCK) 23 October 1997 (1997-10-23) page 4, line 21 -page 5, line 29; claim 24 --- -/--	1-44, 48-54

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2004	21. 12. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	YVONNE SIÖSTEEN / ELY

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDE[redacted]O BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GALINA SKLADCHIKOVA ET AL: "Extracellular adenosine triphosphate affects neural cell adhesion molecule (NCAM-mediated cell adhesion and neurite outgrowth" JOURNAL OF NEUROSCIENCE RESEARCH, vol. 57, 1999, pages 207-218, XP002284206 page 215, right column, line 1 - line 40 and especially line 17 (AENQQGUS), abstract	1-44, 48-54
A	WO 91 00916 A (UNIV CALIFORNIA) 24 January 1991 (1991-01-24) page 5, line 16 - line 25 page 25, line 9	1-44, 48-54
A	WO 01 96364 A (IMP COLLEGE INNOVATIONS ;KING S COLLEGE LONDON (GB); SAFFELL JANE) 20 December 2001 (2001-12-20) the whole document	1-44, 48-54
A	US 6 255 454 B1 (BARR PHILIP J ET AL) 3 July 2001 (2001-07-03) column 3, line 8 - line 30	1-44, 48-54
A	LARS C. B. RONN ET AL: "Neurite outgrowth induced by a synthetic peptide ligand of neural cell adhesion molecule requires fibroblast growth factor receptor activation" JOURNAL OF NEUROCHEMISTRY, vol. 75, 2000, pages 665-671, XP002284207 the whole document	1-44, 48-54
A	PHILIPP NIETHAMMER ET AL: "Cosignaling of NCAM via lipid rafts and the FGF receptor is required for neuritogenesis" THE JOURNAL OF CELL BIOLOGY, vol. 157, no. 3, 29 April 2002 (2002-04-29), pages 521-532, XP002284208 ISSN: 0021-9525 the whole document	1-44, 48-54
A	WO 00 11204 A (LANAHAN ANTHONY A ;BENEKEN JUTTA (US); TU JIAN CHENG (US); WORLEY) 2 March 2000 (2000-03-02) the whole document	1-44, 48-54

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C.(Continuation) DOCUMENTS CONSIDE[redacted] BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FERDYNAND J KOS ET AL: "Costimulation of T cell receptor-triggered IL-2 production by Jurkat T cells via fibroblast growth factor receptor 1 upon its engegament by CD56" IMMUNOLOGY AND CELL BIOLOGY, vol. 80, 2002, pages 364-369, XP002284209 the whole document ---	1-44, 48-54
A	DATABASE EBI [Online] 1 November 1996 (1996-11-01) retrieved from EMBL Database accession no. Q61945 XP002297229 93% identity in 14aa/49aa with SEQ ID NO 9 & SANTONI, M.J. ET AL: "Differential exon usage involving an unusual slicing mechanism generates at NCAM cDNA in mous brain" EMBO J., vol. 8, 1989, pages 385-392, -----	1-44, 48-54

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00901

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-24
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 1-3, 14-25, 29-44 and 54
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[X] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-44 and 48-54 (all partly)

directed to a method of modulating the interaction between a fibroblast growth factor receptor and a protein having a binding site comprising SEQ ID NO:1 (NCAM Fn III, FGFR binding motif) and a method of finding compounds which interact with FGFR and a polypeptide comprising the sequence SEQ ID NO: 1.

Invention 2: 1-54 (all partly)

directed to a method of modulating the interaction between a fibroblast growth factor receptor and a protein having a binding site comprising SEQ ID NO2 (Interleukin-6 receptor beta chain, FGFR binding motif) and a method of finding compounds which interact with FGFR and a polypeptide comprising the sequence SEQ ID NO: 2.

Inventions 3-146: claims 1-54,
all partially and as far as applicable.

Subject-matter essentially as defined above for invention 2, but limited to the respective SEQ.ID s 3-146, whereby invention 3 relates to SEQ ID NO:2, invention 3 to SEQ ID NO:3, etc and invention 146 relates to SEQ ID NO:146.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1-24

Although claims 1- 24 are directed to a method of treatment of the human/animal body, to the extend that they pertain to in vivo use, a search has been carried out, based an the alleged effects of the compound for the parts of the claims which belong to invention 1 and which appear to be clear, supported and disclosed.

Continuation of Box I.2

Claims Nos.: 1-3, 14-25, 29-44 and 54

Present claims 1-3, 14-25, 29-44 and 54 relate to methods using a compound defined by reference to a desirable characteristic or property, namely using a compound being a functional cell-surface receptor, or using a compound comprising at least two immunoglobulin (Ig)-like domains and/or at least two fibronectin type 3 (F3) domains or at least one Ig-like and one F3 domain . Claim 22 refer to a method using a compound being a functional cell-surface receptor and another protein being characterized by having a binding site consisting of one or more "strand-loop-strand" structural motifs. Claims 1, 45 and claims dependent of these claims lack clarity because of the expression "fragments, variants or homologues therefof. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the method using fibroblast growth factor receptors and a polypeptide having a FGFR binding site comprising SEQ ID NO 1 have been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat[illegible] Application No
PCT/D[illegible]/00901

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 03016351	A	27-02-2003	CA	2457164 A1	27-02-2003
			WO	03016351 A2	27-02-2003
			EP	1434798 A2	07-07-2004
WO 9738708	A	23-10-1997	EP	0991422 A1	12-04-2000
			JP	2001519765 T	23-10-2001
			WO	9738708 A1	23-10-1997
WO 9100916	A	24-01-1991	AT	179862 T	15-05-1999
			AU	638734 B2	08-07-1993
			AU	6077990 A	06-02-1991
			CA	2063431 A1	07-01-1991
			DE	69033109 D1	17-06-1999
			DE	69033109 T2	18-11-1999
			DK	481000 T3	15-11-1999
			EP	0481000 A1	22-04-1992
			ES	2133271 T3	16-09-1999
			HU	61052 A2	30-11-1992
			JP	4506604 T	19-11-1992
			KR	235266 B1	15-12-1999
			NO	920060 A	02-03-1992
			SG	72657 A1	23-05-2000
			WO	9100916 A2	24-01-1991
			US	5707632 A	13-01-1998
			US	6355440 B1	12-03-2002
			US	6350593 B1	26-02-2002
			US	6384191 B1	07-05-2002
WO 0196364	A	20-12-2001	EP	1294744 A2	26-03-2003
			WO	0196364 A2	20-12-2001
			US	2004102370 A1	27-05-2004
US 6255454	B1	03-07-2001	US	5229501 A	20-07-1993
WO 0011204	A	02-03-2000	AU	772105 B2	08-04-2004
			AU	5779899 A	14-03-2000
			EP	1105734 A2	13-06-2001
			JP	2002523056 T	30-07-2002
			WO	0011204 A2	02-03-2000
			US	2003170807 A1	11-09-2003
			US	6720175 B1	13-04-2004